TRANSACTIONS OF THE AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION, VOL. 117, 2006

PRESIDENT'S ADDRESS: MOTHER WAS RIGHT: THE HEALTH BENEFITS OF MILK OF MAGNESIA

MARSHALL A. WOLF, M.D.

My mother had three basic tenets in terms of her beliefs about health care:

1. Eggs, whole milk and "good" bread with butter, consumed daily, are the basic elements of a healthy diet.
2. A heavy waterproof garment, preferably one which completely obscures your body habitus and sexual identity, and waterproof footwear, will diminish both the severity and frequency of upper respiratory infections.
3. Recovery from all illness is facilitated by milk of magnesia.

Since you are all familiar with modern nutritional data and the cardiovascular risks of foods rich in cholesterol and saturated fat, I will not elaborate on the first of these except to remind you of the comment of a great modern sage, Woody Allen: "why is everything that was good for us when we were children bad for us now?"

When I was at NIH, volunteers, half warm and dry, and half splashed with cold water, the windows left open to subject them to a cold breeze, were exposed to rhinovirus. The frequency and severity of illness was similar in both groups. Although I was then in my mid-twenties, my mother was still calling to remind me to dress appropriately for inclement weather. When I told her of these results, hoping to gain respite from her calls, she remarked: "what do they know".

My and my siblings' response to my mother's faith in the curative properties of milk of magnesia was to avoid lactescent beverages when ill. The wisdom of her recommendation completely escaped me until many years later, when I encountered a puzzling and challenging patient.

LA was a 67-year-old nationally prominent business executive and the mother of 2 who transferred to our hospital after sustaining a cardio-respiratory arrest.

She was in good general health. Her mother had died suddenly at age 63 and had had a history of an enlarged heart of unknown cause. The patient's own past history included an episode of hyperthyroidism 15 years prior to admission treated with radioactive iodide. She had subsequently been maintained on Euthroid-3. She had had occasional bronchospasm since childhood treated with inhaled bronchodilators.

Her cardiac history began 4 years prior to her admission when she presented with a one day history of palpitations. Her EKG showed atrial fibrillation. Her physical examination was remarkable only for a systolic ejection click with a 2/6 mid-to-late systolic ejection murmur. Her T4 was 12 μg/dl and she was switched from Euthroid-3 to Synthroid 0.15 mg daily. She was treated with digoxin and reverted to sinus rhythm in 24 hours. She was maintained on this medication for 2 months; it was then discontinued.

She did well for the following 3 years until one year prior to admission when she doubled her Synthroid in an effort to lose weight. She re-presented with atrial fibrillation which again was treated with digoxin with reversion to sinus rhythm.

Six months prior to admission she experienced a syncopal episode. She had been using her albuterol inhaler frequently as well as taking digoxin for palpitations. Her physical examination was unchanged. She was in sinus rhythm when she presented. Holter monitoring and an exercise tolerance test showed only occasional APB's and VPB's.

She remained well until 6 days prior to admission when she once again developed palpitations. Her physician husband gave her 3.5 mg digoxin over 24 hours. She became weak and anorectic and then collapsed. He resuscitated her and managed to get her to a local hospital where she was allegedly in ventricular fibrillation. She was defibrillated and then treated with lidocaine and bretylium. Her digoxin level rose to 4.3 ng/ml. Over the next 4 days she continued to have ventricular irritability despite lidocaine and procainamide. Congestive heart failure was suspected and she was diuresed but did not improve. She was then transferred to our hospital.

Her physical exam was normal with the exception of the murmur noted previously. Her EKG showed non-specific ST-T abnormalities. Her digoxin level was 2.7 ng/mL. Potassium was 3.8 mmol/L.

Over the next several days her digoxin level fell to less than 0.5 ng/mL. She continued to demonstrate runs of nonsustained ventricular tachycardia and supraventricular tachycardia. She was taken to the electrophysiology testing laboratory where nonsustained polymorphous ventricular tachycardia was evoked by 2 extrasystoles. Fab fractions were used to wash out her digoxin; she continued to demonstrate ventricular irritability. This did not improve with tocainide.

At this point, her magnesium level was noted to be 1.3 (1.7–2.5) mg/dl. She was treated with 2 grams of intravenous magnesium sulfate and her ventricular irritability markedly diminished. The next day, after receiving an additional 2.5 grams of magnesium sulfate, she was restudied. No ventricular arrhythmias were inducible.

In an effort to explain her hypomagnesemia, a more detailed history was obtained. She denied excess alcohol intake. Her husband said he was not sure how much she drank but "her closet was filled with empty whiskey bottles".

She discontinued alcohol. On magnesium oxide, 4 grams per week, she had no further episodes of arrhythmia for the next 3 years. At that time she began drinking again. 2 months later she had a cardiovascular arrest and could not be resuscitated.

When I encountered this patient, I realized I did not know much about magnesium. In retrospect, I only recognized one of the seven factors in her history which contributed to her magnesium deficiency, her alcoholism, and only one of the several ways in which alcohol causes magnesium deficiency, increased renal magnesium loss. I was also unaware of the relationship between magnesium deficiency and atrial fibrillation.

Despite my personal ignorance, magnesium had long been recognized to be of biologic importance. Magnesium had been shown to be an essential element for plants in 1860 and for mammals in 1926. In 1929, magnesium supplementation cured staggers (grass tetany) in cattle. In 1934 Hirschfelder and Haury described the symptoms of severe magnesium deficiency in man. These included tremors, clonic jerks, convulsions, ataxia and nystagmus; carpal pedal spasm; apathy, delirium and coma; dysphagia due to esophageal spasm; ileus; hypocalcemia which was responsive to magnesium repletion; hypokalemia responsive to magnesium repletion and resistant to potassium repletion; as well as arrhythmia. The next year Zwillinger (1) reported the termination of arrhythmias, presumed due to digitalis intoxication, with pharmacologic doses of magnesium.

After calcium, magnesium is the most abundant divalent cation in the body. The average adult has 25 grams of this element. About half is intracellular, most of it being bound to ATP. Most of the rest is in bone, a third of which is exchangeable with serum and provides the buffer to maintain serum levels in the physiologic range. The serum itself contains less than 1% of the body's magnesium, about 60% of which is free, a third bound to serum proteins, primarily albumin, and 6% complexed with anions (2). Magnesium is involved in the regulation of enzyme activity, especially those enzymes requiring ATP, more than 300 different systems having magnesium as a co-factor. In cardiac, skeletal and smooth muscles it modulates tension development. Changes in intracellular magnesium content have a profound effect on the transmembrane ion channels for sodium, potassium and calcium.

Magnesium is common in our diet; nuts, dried fruit, whole grains, green leafy vegetables and shellfish being the main sources of our magnesium. A third to half of magnesium is absorbed, some passively and some actively, this latter component being increased in individuals who are magnesium deficient. Most of this active absorption occurs in the distal small bowel. Magnesium is excreted by the kidneys; the exact mechanism of magnesium regulation is still somewhat obscure. In magnesium deficient patients excretion can be reduced to 10 to 20 mg per day; there does not seem to be a clear maximum for magnesium excretion. Of the magnesium filtered, about a quarter is reabsorbed in the proximal tubule and the remainder in the thick ascending limb of Henle.

Many, if not most of us, are magnesium deficient unless we supplement our dietary intake. The causes of this are multiple; I remember them by thinking of the D's of magnesium deficiency.

The first D is diet. The Institute of Medicine has recommended a dietary intake of 420 mg. per day for adult males and 320 mg. per day for adult females. Recent studies have suggested that the average American male takes in 325 mg. of magnesium per day and the American female approximately 228 mg. Furthermore, the amount of magnesium in our diet continues to decrease. The average American diet fifty years ago contained almost twice as much magnesium as does our present diet. A major factor leading to this decline is our preference for processed foods; white rice has one-sixth the magnesium content of brown rice and corn flakes have less than one-tenth of the magnesium content of oatmeal (3).

The second D is drink. Alcohol alters magnesium balance in several ways: there is decreased magnesium in the diet of most alcoholics; alcohol impairs absorption of magnesium from the gastrointestinal track; and finally, and most importantly, alcohol, even in moderation, causes an increase in renal magnesium loss.

The third D is diarrhea. By this I mean gastrointestinal problems in general, including inflammatory bowel disease, laxative abuse, vomiting, nasogastric suction, short bowel syndromes and malabsorption.

The fourth D is diuretics. This includes the use of diuretics, both osmotic and pharmacologic, as well as kidney disease. All acute and chronic renal problems cause a dysregulation of magnesium handling by the kidney, most renal problems in their early stages leading to excess magnesium loss and in their later stages, to decreased ability to clear magnesium loads. Increased renal loss has been documented in Bartter's and Gitelman's syndromes, in patients with increased sodium or potassium excretion, and finally, in patients with hypercalcemia who have decreased reabsorption of magnesium in the ascending loop of Henle.

The fifth D is drugs. Multiple medications have been shown to increase renal magnesium loss including albuterol and other beta agonists, aminoglycoside antibiotics, carbenicillin, ticarcillin, digitalis, amphotericin B, pentamadine, cisplatin and cyclosporine.

The sixth D is disease. Foremost among these is diabetes, but magnesium deficiency is also seen in hyperthyroidism, hyperaldosteronism, and hypercalcemia of any cause.

The last D is diaphoresis. Sweat contains magnesium and excess loss through this mechanism is the reason runners cramp up.

In retrospect, there were multiple factors contributing to my patient's magnesium deficiency. These included: her diet; her alcoholism, which decreases magnesium absorption and increases renal magnesium loss; her thyroid overmedication; the effect of digitalis on renal tubular magnesium reabsorption; her use of diuretics and sympathomimetics; the intravenous fluids she was given during her hospitalization which did not contain any magnesium supplementation; and finally, the stress of both her hospitalization and withdrawal from alcohol.

The prevalence of magnesium deficiency is often underestimated because of the poor correlation between serum and tissue levels. Numerous studies have demonstrated that the serum level is an inaccurate indicator of the magnesium level in muscle in general and in heart muscle in particular. The test which best demonstrates magnesium deficiency is measurement of the fraction of an administered magnesium load which is retained over the next 24 hours (4). The need to collect 24 hour urines has made this more of a research tool than a clinical tool. Interestingly, despite the poor correlation between serum and tissue magnesium, almost all studies of "magnesium deficiency" use serum levels.

Symptoms are often a better indicator of a patient's magnesium deficiency then the serum level. Night cramps and, less often, Raynaud's phenomenon (5), are clues that a patient's magnesium is depleted. Other clinical clues are otherwise unexplained hypokalemia and hypocalcemia. Those patients taking diuretics, whose serum potassium remains low despite heroic replacement doses of potassium, are almost always magnesium deficient; repletion of magnesium in such patients usually results in a prompt restoration of the serum potassium level.

Repletion of a magnesium deficit requires prolonged magnesium supplementation. While serum levels may respond to a bolus of 1–2 grams of magnesium sulfate, repletion of the tissue compartments requires 2 to 4 weeks of therapy. 250–300 mg of oral magnesium, usually as the oxide or gluconate, one to three times daily, is an effective and usually well-tolerated regimen. In patients with normal renal function, renal excretion prevents hypermagnesemia. The laxative effective seen in occasional patients can be eliminated by reducing the dose or switching to the more expensive chloride salt.

Before I became a real physician, I was an academic cardiologist. Today I would like to restrict my comments to the various ways in which magnesium deficiency manifests itself in patients with cardiovascular problems. I will not review its benefits in patients with osteoporosis and hypertension nor its possible benefits in preventing adult-onset diabetes, atherosclerosis and sudden death.

Magnesium deficiency does change the EKG. In animal studies, it usually presents as tall tented T waves mimicking hyperkalemia; I have only seen two patients with that pattern. Usually it has the appearance of low T waves with a slightly prolonged QTc interval suggestive of the hypokalemia with which it is usually associated. Occasionally in severe magnesium deficiency one sees T wave alternans (Figure 1), an EKG finding seen in patients destined to develop polymorphous ventricular tachycardia as well as those with the inherited channelopathies associated with premature sudden death.

Although magnesium has a number of important effects on the metabolism of both nerve and muscle, its importance in cardiovascular arrhythmias is probably the result of its effect on membrane stability and the effect of its deficiency on both membrane permeability and neuro-muscular excitability. Deficiency of this element is associated with increased intracellular calcium levels as well as decreased intracellular potassium levels. Furthermore, in pharmacologic doses, mag-

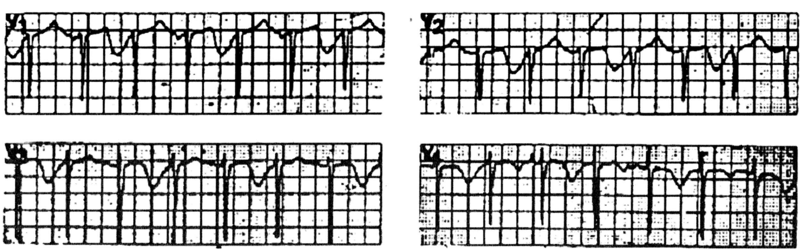

FIG. 1. T wave alternans. In contrast to electrical alternans, in which the QRS complexes alternate, in T wave alternans the QRS complexes are unchanging and the T waves alternate. This pattern is associated with increased risk of polymorphous ventricular tachycardia.

nesium increases sinoatrial conduction time, the PR interval, and also the refractory period of the AV node.

There are a few arrhythmias for which magnesium deficiency may be causal and/or repletion has shown to be effective. There are other arrhythmias where magnesium has been used but where causality is less certain although magnesium repletion has been efficacious, such as the ability of pharmacological doses of magnesium to decrease the frequency of both atrial and ventricular premature beats as well as to terminate re-entry tachycardias and occasionally monomorphic ventricular tachycardia. The two arrhythmias which are often due to magnesium deficiency and respond to magnesium repletion are polymorphous ventricular tachycardia (PVT) and multifocal atrial tachycardia (MAT).

Polymorphous ventricular tachycardia is, while uncommon, of great importance, since it is often fatal and very treatable. It is the arrhythmia seen in patients with congenital QTc interval prolongation and sudden death. It also occurs in a variety of situations in which the QTc interval is prolonged and the heart rate is slow, including the proarrhythmic effect of many type I anti-arrhythmic drugs, hypothyroidism, as well as in patients taking pentamidine, erythromycin and psychotropic drugs including the antidepressants, phenothiazines and lithium. When this arrhythmia was first recognized many years ago it was often referred to as paroxysmal ventricular fibrillation. In Zwillinger's first description (1) of the use of magnesium to revert arrhythmias, several of the arrhythmias were polymorphous ventricular tachycardia. Case reports associating severe magnesium deficiency with this arrhythmia are not new, the problem initially being observed in severe alcoholism. Studies have shown this arrhythmia is often due to increased early afterdepolarization-induced triggered activity and that this arrhythmia is reversible by magnesium supplementation. In patients with congenital QTc interval prolongation, the pathophysiologic defect is usually a problem with sodium or potassium transport, a problem also seen in patients with severe magnesium deficiency. Tzivoni and his collaborators (6) treated a series of patients with PVT and QTc prolongation and demonstrated a uniform response to magnesium repletion. This variant of PVT, torsades de pointes, is far more common than the PVT seen with a normal QTc interval in which magnesium is ineffective.

Multifocal atrial tachycardia is an arrhythmia often confused with atrial fibrillation. By definition it is an atrial tachycardia which has at least 3 different P wave morphologies, varying PR intervals and varying R-R intervals. First described by Burch, it was usually associated with hypokalemia and/or diabetes. In Ken Shine's seminal paper, the association with pulmonary disease was noted as well as the poor efficacy and frequent toxicity of digitalis in such patients. Iseri (7) reported a series of patients with this arrhythmia who had a dramatic response to magnesium infusions with prompt resolution of their arrhythmia; he also showed, with balance studies, that these patients were magnesium deficient. In retrospect we know that diabetes and hypokalemia as well as the medications used to treat pulmonary insufficiency including theophylline, beta agonists and diuretics, all are associated with magnesium deficiency. The sensitivity of these patients to digitalis drugs is also explained on the basis of the known increase in digitalis toxicity in patients with magnesium deficiency.

PVT and MAT are relatively rare arrhythmias; atrial fibrillation is not. Since 6% of patients in their 70's and 14% of patients in their 80's have this as their dominant rhythm, it is likely that several of you in this room are fibrillating. Several years ago, at one of these meetings, I was asked to consult on one of our members who had an episode of his paroxysmal atrial fibrillation; magnesium repletion markedly decreased the frequency of his subsequent episodes.

Although magnesium in pharmacologic doses was successful in reverting occasional patients with atrial fibrillation to sinus rhythm, one of the first studies linking these two phenomena was that of DeCarli (8) who noted that 20% of patients presenting with new onset atrial fibrillation were hypomagnesic and furthermore that these patients were resistant to the effects of digoxin, requiring on average twice as much digoxin to achieve slowing than patients who were normomagnesemic. The frequent association of alcohol abuse and atrial fibrillation may well be the result of magnesium deficiency.

I would like to share with you two cases which demonstrate important interactions between this arrhythmia and magnesium deficiency.

The first was that of a 57 year old woman, a "social drinker", who underwent an exploratory laparoscopy for what turned out to be a benign ovarian lesion. Ten hours postoperatively she developed atrial fibrillation with a narrow QRS complex and a ventricular rate of 180. Over the course of 2 hours she was given digoxin 0.75 mg. intravenously and verapamil 15 mg. intravenously. Her ventricular rate did not slow. She was then given magnesium sulfate 2 grams intravenously over 2 minutes and, over the next minute, slowed and then reverted to sinus rhythm. Her magnesium level was 1.2 (1.7–2.5) mg/dl. She was taking hydrochlorthiazide for hypertension and her "social drinking" consisted of 16 to 20 ounces of rye whiskey per day.

The second patient was a 46 year old engineer with Crohn's disease who had had recurrent atrial fibrillation with poor rate control despite vigorous dosing with both verapamil and digoxin. His cardiologist then suggested AV nodal ablation in order to achieve rate control. His physician/wife, hoping to avoid a permanent pacemaker, sought a second opinion. His failure to respond to both verapamil and digoxin, his chronic diarrhea and severe night cramps, suggested he might be magnesium deficient. He had had one magnesium level drawn which was low; he had never been prescribed magnesium. He was repleted orally. He noted initially that his ventricular rate, when in atrial fibrillation, was much slower. After about a month of repletion, his episodes of atrial fibrillation ceased and he was free of this arrhythmia for about 3 years, the first time since his problem began had he ever gone more than 5 days without a recurrence.

Finally, I would like to discuss a few of the interactions between magnesium deficiency and coronary heart disease. Magnesium deficiency has been shown to be associated with an increased likelihood of sudden death. In localities where the magnesium content of the water is high, sudden death is less frequent than in regions that have a low magnesium concentration in the drinking supply. In addition magnesium levels in the hearts of victims of sudden death are lower than in the hearts of individuals who die of other causes. Animal studies suggest that animals on an atherogenic diet who are magnesium deficient develop much more severe disease than those on a similar diet who receive magnesium supplementation.

Although not a frequent cause of coronary ischemia, variant angina due to coronary artery spasm, often unrelated to exercise and associated with ST elevation rather than ST depression, is also magnesium responsive. In clearance studies these patients retained 60% of a magnesium load compared to 36% in control patients (9). Furthermore, in those patients with this problem who had their symptoms brought on by either hyperventilation or exercise (10), magnesium was noted to have a significant beneficial effect.

The effect of magnesium in patients with acute myocardial infarction provides us with lessons that are relevant to medicine in general in addition to this problem in particular. Early studies of animals and patients with acute myocardial infarction demonstrated that they often had transient hypomagnesaemia. They also had decreased myocardial magnesium levels as well as increased myocardial calcium levels; both could be prevented by magnesium infusion. There followed a series of clinical trials, controlled but small, which suggested that if patients were given intravenous magnesium when they first presented with suspected myocardial infarction, cardiac morbidity and mortality were significantly reduced. A series of such studies showed a consistent decrease in severe arrhythmias, conduction disturbances and mortality, the benefit being similar in magnitude to that achieved with lytic therapy. The first large study of this, the LIMIT-2 study of 2300 patients, showed a significant though less marked decrease in cardiac mortality than that seen in the multiple small studies described above. It was thought that this decreased benefit was because the LIMIT-2 study patients also received thrombolytic agents, beta blockers and antiplatelet medications. A major dilemma, the so called "ISIS Crisis", then occurred, when the ISIS-4 study of 60,000 patients (11), showed a slightly increased mortality in the sub-group treated with magnesium. Extensive analysis of the difference between the early small studies which had achieved a 50% reduction in mortality, the LIMIT-2 study which showed about a 25% decrease in mortality and the ISIS-4 study which had shown a slight increase in mortality, suggested that the important variable was the timing of the magnesium therapy, very early therapy being required for benefit. Elliot Antman, a member of this society, then did the definitive study. 6213 patients with acute myocardial infarction were given magnesium therapy or placebo on presentation; no benefit was found (12).

Although, as a magnesium maven, I was personally disappointed in the results, I thought it provided an important lesson: it is very important to critically evaluate our therapies. Antman and his colleagues demonstrated, in this instance, as in recent studies of Vitamin E and hormone replacement therapy, that therapies based on our understanding of pathophysiology, may have little benefit, and indeed some risk, when given to patients.

So what are the take home messages from this talk?

1) *Most patients are magnesium deficient (and most of us are someone's patient).*
2) *You know that patients are magnesium deficient if they have night cramps and should suspect that they are if they have Raynaud's and no cryoglobulinemia.*
3) *Those patients who require heroic doses of potassium replacement as well as those resistant to calcium channel blockers are probably magnesium deficient.*
4) *Serum levels correlate poorly with tissue levels and are often misleading.*
5) *Magnesium deficiency is often causative in multifocal atrial tachycardia and polymorphous ventricular tachycardia with a prolonged QTc interval.*

6) *Magnesium deficiency may be causative in atrial fibrillation and may be the reason that achieving rate control in some patients with this arrhythmia is difficult.*
7) *Magnesium replacement is often effective in decreasing extra systoles and occasionally in preventing/terminating reentrant arrhythmias.*
8) *Magnesium supplementation may be effective in reducing the incidence/severity of osteoporosis, adult-onset diabetes, hypertension, and sudden death.*
9) *Sometimes mother does know best.*

BIBLIOGRAPHY

1. Zwillinger L. Uber Die Magnesiumwirkung Auf Das Herz. Klinische Wochenschrift. 1935;14:1429–1433.
2. Rude RK. Magnesium Deficiency: A Cause of Heterogenous Disease in Humans. Jour of Bone and Mineral Research. 1998;13:749–758.
3. Elin RJ. Magnesium Metabolism in Health and Disease. DM. 1988;34:161–219.
4. Ryzen E, Elbaum N, Singer FR, Rude RK. Parenteral Magnesium Tolerance Testing in the Evaluation of Magnesium Deficiency. Magnesium. 1985;4:137–147.
5. Vogelzang NJ, Torkelson JL, Kennedy BJ. Hypomagnesemia, Renal Dysfunction, and Raynaud's Phenomenon in Patients Treated with Cisplatin, Vinblastine, and Belomycin. Cancer. 1985;56:2765–2770.
6. Tzivoni D, Banai S, Schuger C, Benhorin J, Keren A, Gottlieb S, Stern S. Treatment of Torsades de Pointes with Magnesium Sulfate. Circulation. 1988;77:392–397.
7. Iseri LT. Magnesium and Cardiac Arrhythmias. Magnesium 1986;5:111–126.
8. DeCarli C, Sprouse G, Larosa JC. Serum Magnesium Levels in Symptomatic Atrial Fibrillation and Their Relation to Rhythm Control by Intravenous Digoxin. The Amer Jour of Cardiology. 1986;57:956–959.
9. Goto K, Yasue H, Okumura K, Matsuyama K, Kugiyama K, Miyagi H, Higashi T. Magnesium Deficiency Detected by Intravenous Loading Test in Variant Angina Pectoris. The Amer Jor of Cardiology. 1990:709–712.
10. Kugiyama K, Yasue H, Okumura K, Goto K, Minoda K, Miyagi H, Matsuyama K, Kojima A, Koga Y, Takahashi M. Suppression of Exercise-Induced Angina by Magnesium Sulfate in Patient with Variant Angina. JACC. 1988;12:1177–1183.
11. ISIS-4: A randomized factorial trial assessing early oral captopril oral monitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. The Lancet. 1995;345:669–685.
12. Magnesium in Coronaries (MAGIC) trial investigators. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the Magnesium Coronaries (MAGIC) trial: a randomized controlled trial. Lancet. 2002;360:1189–1196.